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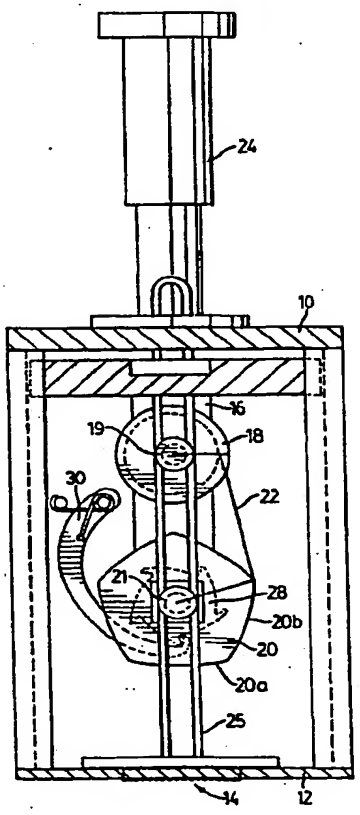
(54) Title: METHOD AND APPARATUS FOR ACCESSING MAMMALIAN SKIN LOCATIONS BELOW THE STRATUM CORNEUM

(57) **Abstract**

A device for removing a substantial amount of the stratum corneum from a defined area of a patient's skin surface as provided, for use prior to application to the defined area of a transdermal drug delivery device. The device includes a first rigid frame (10) with a bottom plate having a central aperture through which the area to be treated is exposed when the device is placed against the skin in use. A second frame (16) slidably mounted with respect to the first carries a reel (18) of outwardly adhesive film and a movable applying surface over which the adhesive film passes and advances intermittently. By repeated extension and retraction of the movable frame an appropriate number of times, the stratum corneum may be substantially completely removed from the selected area and a transdermal drug delivery device subsequently applied thereto.



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METHOD AND APPARATUS FOR ACCESSING MAMMALIAN SKIN LOCATIONS BELOW THE STRATUM CORNEUM

This invention relates to apparatus for effecting the partial or complete removal of the stratum corneum thickness at a defined area of a mammalian patient's skin surface and to a process for using such apparatus to prepare the skin for the transdermal delivery of drugs.

Transdermal drug delivery is delivery of a therapeutic agent through the skin of a patient, for distribution of therapeutic agent within the body by the circulation of the blood. The therapeutic agent can be for general or localized treatment purposes. After passing through the outer layers of skin, the drug diffuses into the capillaries or tiny blood vessels in the skin, and thence to the circulating blood. Additionally, after having diffused into the skin, the drug may enter into the lymphatic system and thence to the circulating blood. Transdermal drug delivery is to be contrasted with topical drug delivery, which is generally considered to be delivery to a topical wound, lesion, area affected by a skin disorder, etc., of a medicament for the purposes of combatting infection, accelerating wound healing, relieving pain, managing skin disorders etc., by treatment of the localized area.

Mammalian skin comprises a number of layers. The

lowermost layer is the dermis, which consists of a fibrous layer of collagen and other material. Overlying the dermis is the epidermis, which consists of a series of layers of living epidermal cells in various stages of maturity. The degree of maturity increases with the distance of the layer from the dermis. The epidermal layer which is most remote from the dermis and forms the outermost layer of skin is called the stratum corneum. It is comprised of a keratinized layer of dead, flattened epidermal cells. The stratum corneum is the principal barrier to ingress of foreign materials into the body. The stratum corneum is continuously shed by the body, and continuously reformed with keratinized epidermal cells from the layers below.

Because of its effectiveness as a protective barrier, transdermal drug delivery has, for the most part, been confined to the delivery of relatively low molecular weight and relatively non-polar therapeutic agents, and accordingly, has not been useful in practice with a large number of effective therapeutic agents. The stratum corneum has in the past been regarded as a reservoir into which the transdermally administered drug deposits, for subsequent diffusion into the body (see Bronaugh and Maibach "Percutaneous Absorption", Marcel Dekker, Inc., New York).

Various means are currently known to increase the permeability of the stratum corneum. These include the use

of skin penetration enhancers, e.g. AZONE (trademark) (1-dodecylhexahydro-2H-azepin-2-one); iontophoresis, in which an electrical field is used to create a weak current across the stratum corneum to accelerate the penetration of ionic drugs; sonophoresis, in which ultrasound assists the passage of the drugs across the skin interfaces; and electroporation, in which electrical currents create temporary pathways through the skin.

U.S. Patent No. 4,883,668 Ohta, issued November 28, 1989, discloses an article comprising a support and a substance capable of removing stratum corneum uniformly distributed on the support in small discontinuous areas, for use in removing a portion of the stratum corneum prior to transdermal drug administration. The removing substance is suitably a pressure sensitive adhesive. The drug is subsequently applied for transdermal delivery through the treated area of skin, by putting a plaster on the skin or by iontophoresis.

It is desirable that any compromising of the stratum corneum prior to application of transdermal drug delivery devices thereto should be done in a careful, controlled manner. Excessive or sudden, harsh removal of stratum corneum can cause pain to the patient. A proper treatment to remove, in whole or in part, the stratum corneum calls for the initial selection of a skin area, followed by the successive application to that area of a

removal device such as an adhesive film, so that each such application removes a small thickness portion of the stratum corneum. The device should be applied repeatedly and reproducibly to the same, preselected area of skin surface, until it has been determined that the appropriate amount of stratum corneum has been removed in this manner. Any procedure involving successive application and removal of adhesive sheets to prepare an area of skin for a drug delivery device be as reproducible as possible, in both delimiting the area of skin from which a portion of stratum corneum is removed in each stripping step and in the depth of stratum corneum removed after a given number of such steps.

It is an object of the present invention to provide a compact device for carrying out the adhesive stripping of stratum corneum with a high degree of reproducibility.

It is a further object of the present invention to provide such a device which is operable to effect a desired number of consecutive stripping procedures on a fixed area of the skin without removal of the device from the treatment area.

It is a still further object of the present invention to provide such a device which may conveniently be applied by a patient to his own body using one hand.

The present invention provides, according to one aspect thereof, an apparatus for removing in a controlled fashion, at least a portion of the stratum corneum from mammalian skin in a predetermined location, without causing undue pain or irritation to the patient, prior to transdermal drug delivery through the predetermined area. Compactness and ease and reproducibility of operation of the device make it suitable for use by the patient himself, where the presence of a clinician is not otherwise necessary.

The device includes a first rigid frame with a bottom plate having a central aperture through which the area to be treated is exposed when the device is placed agains the skin in use. A second rigid frame movably mounted with respect to the first carries a reel of outwardly adhesive film which extends over an applicator having an applying surface, and a take-up device for the film after passage over the applying surface. When the second rigid frame is advanced towards the patient's skin to its fullest extent, the adhesive film surface along the applying surface comes into contact with the exposed predetermined skin location below the aperture in the bottom plate, and a portion of the stratum corneum adheres thereto and is removed when the second rigid frame is

retracted. Associated with the two frames and the reel or roller is an appropriate means for advancing the adhesive film over the applying surface so that for each movement of the second frame to its retracted position, an entirely fresh adhesive surface of the adhesive film is exposed through the aperture. In one embodiment, this is a ratchet-and-pawl or other suitable mechanism operable positively to turn the reel or take-up device, when the second frame is again extended, a suitable amount to apply fresh tape to the applying surface.

In one preferred embodiment according to the present invention, the take-up device is a roller journalled in the second said frame. This can be driven to pull the adhesive film off the storage reel and over the applying surface, e.g. by use of a ratchet and pawl mechanismoperated when the two frames are moved relative to one another. Alternatively, it can driven by a motor preset to operate to advance the predetermined length of adhesive film on each manual actuation of the motor.

Also according to a preferred embodiment, the roller constituting the take-up device can be provided with a plurality of rectangular peripheral edge faces, of similar size, so that the roller as axially viewed exhibits polygonal symmetry. Each said rectangular face constitutes an applying surface, and they are brought successively into registry with the aperture in the bottom plate as the

roller is rotated.

In another preferred embodiment, the take-up roller is separate from the applicator, and is journalled onto the second frame at a position downstream therefrom. Then the applicator can be in the form of a plunger attached for movement with the second frame, with the lowermost surface thereof being generally rectangular and constituting the applying surface of the device.

Specific preferred embodiments of the present invention are illustrated in the accompanying drawings, in which:

FIGURE 1 is a schematic view from one side of apparatus according to a first preferred embodiment of the present invention, with the operating mechanism in the rest (retracted) position;

FIGURE 2 is a like view of the apparatus of FIG 1, but with the operating mechanism in an intermediate (partially extended) position;

FIGURE 3 is a like view of the apparatus of FIG 1 and FIG. 2, but with the operating mechanism in its fully extended (skin contacting) position;

FIGURE 4 is a partial cross-sectional view of the

apparatus of FIG.1 seen at right angles to the view of FIG. 1;

FIGURE 5 is a diagrammatic cross sectional view of a second preferred embodiment of the present invention, with the frames in the relatively extended position;

FIGURE 6 is a similar view of the embodiment shown in Fig. 5, with the frames in the retracted position;

FIGURE 7 is a view similar to Fig. 6, of a third preferred embodiment according to the invention.

Figures 1 to 4 of the accompanying drawings illustrate apparatus according to a first embodiment of the present invention, including a first rigid frame 10, having a bottom plate 12 with a central rectangular aperture 14. In use, the device is positioned against the skin of a patient so that the selected area from which stratum corneum is to be removed is exposed to the interior of the device through aperture 14.

A second rigid frame 16 is slidably movable with respect to frame 10 in the vertical direction only, i.e. in the direction towards and away from the patient's skin. Frame 16 carries the adhesive film changing mechanism, which in the preferred embodiment here illustrated comprises a cylindrical reel 18 and a parallel roller 20

having a regular polygonal symmetry about its axis of rotation, so that it presents a plurality of equiangularly disposed rectangular faces. A supply of outwardly adhesive film 22 goes around reel 18 and roller 20 and extends between them. As seen in Figure 3, when sliding reel and roller support frame 16 is at its downwardmost (fully extended) position, one horizontally-oriented, tape-covered face 20b of roller 20 is in position to contact the skin of the patient through aperture 14.

The sequence of Figures 1 to 3 shows the operation of the apparatus from the fully retracted (rest) position to the fully extended (skin contact) position of the adhesive film application mechanism. Reel 18 and roller 20 turn respectively about spindles 19 and 21 each fixed at corresponding ends thereof to sliding support frame 16. A downward stroke of the sliding frame is effected by pushing down on handle 24 symmetrically positioned on and affixed to the top of frame 16.

Reel 18 and roller 20 are retained on their spindles and kept from lateral movement, by means of a vertical channel member 25 which is fixed to frame 10 and fits within groove 19a of spindle 19a and groove 21a of spindle 21.

A compression spring 26 telescoped within handle 24 and bearing against the handle and fixed frame 10 impels

retraction of the sliding film support frame when manual pressure is eased off.

Suitable means are included to positively turn reel 18 and unwind adhesive film from roller 20, or to turn roller 20 and wind film onto it from reel 18, over the course of a downstroke of handle 24 by just that angle subended by one rectangular face (20a, 20b, etc.) of the skin-contacting roller, i.e. 360°/n where n is the number of such faces. With each successive extension stroke of handle 24, a fresh adhesive surface is presented through aperture 14 to contact the desired skin contact area.

In this embodiment, positive winding-up rotation of roller 20 to change the present surface 20a to 20b is initiated right at the beginning of the downstroke and completed before face 20b is projected down through aperture 14, by means of the interaction between n-toothed ratchet wheel 28, coaxially affixed to one side of roller 20 for rotation about spindle 21, and spring-loaded pawl 30 affixed to frame 10, as best seen in Figures 1 to 3.

It will be appreciated that any of a number of alternative means might be used for advancing and retracting the sliding frame between its fully retracted and fully extended positions while maintaining bottom plate 12 in contact with the skin and aperture 14 positioned over the area from which removal of stratum corneum is desired.

Likewise, alternative equivalent means will be apparent for stepwise rotation of roller 20 or reel 18 to carry out the changing of the film surface from one extension-retraction stripping operation to the next. It is preferred, however, that the tape winding should occur on the downstroke and not on the upstroke, because as roller 20 is being retracted from the skin, the skin surface exposed through aperture 14 is pulled up a short distance. Any rotation of the roller at that stage could irreproducibly affect the interaction between the adhesive and the stratum corneum. It is readily seen from Figures 1 to 3 that the ratchet-and-pawl mechanism is configured to achieve its desired feature.

Too, it is desirable for compactness of the apparatus overall that rotation of the type advance mechanism commence at or very near the beginning of the downstroke and finish shortly before skin contact with the newly positioned adhesive surface.

The choice of a regular pentagonal symmetry in this preferred embodiment, rather than square, hexagonal or circular angular disposition of faces on roller 20 has been found to afford the optimum trade-off between maximizing the contact face area for a roller of a given overall size, and minimizing the extent to which interfacial edges cut into the film wrapped around the roller. The face

dimensions are typically a 1" x 1" square for preparation of a skin area for subsequent transdermal infusion of drugs.

Other possible modifications to the mechanism of the apparatus include the use of an integral electrical drive means (stepping motor) to advance pentagonal roller 20 by 72° when activated. Such arrangement dispenses with the need for a spring-loaded handle and mechanical elements such as the pawl, to permit a more compact device to be made.

It is preferred that each contact face 20a, 20b, etc. be slightly convexly curved, to minimize the pulling-up of skin as a layer of stratum corneum is removed with retraction of roller 20 on the upstroke of handle 26, and thereby further reduce the inconsistency in the amount of stratum corneum removed in a given number of stripping steps. Irreproducibility may be further reduced by providing the perimeter of aperture 14 with a downwardly projecting, preferably serrated, integral ridge formation 14a which reduces the extent to which skin can be pulled up through aperture 10 in the retraction step of operation of the apparatus.

Adhesion of adhesive film 22 to the reel and roller for smooth operation as they turn may readily be

ensured by fabricating the film as an outwardly adhesive tape having a double-sided adhesive tape against the non-adhesive backing of the skin contacting adhesive film and winding the exposed side of the double-sided adhesive tape about reel 18 or roller 20, whichever functions to take up the advancing adhesive film. It is convenient to provide the reel, roller and tape together as a cassette unit adapted for fitting into the hand-held apparatus. Examples of suitable commercially available skin-coating adhesives and specialty tapes include those sold under the trademarks CO-TRANS (3M Co), MED 116 and MED 118 (Avery Specialty Tape Division), TT 5024-00 and the like from Semex Medical, etc.

Figs 5 and 6 of the accompanying drawings show another preferred embodiment of the present invention. There is a first, upper rigid frame 40 and a second, lower rigid frame 42. Lower frame 42 has a bottom plate 44 with an aperture 46 therein, to define the predetermined area of the patient's skin 48 from which the device is to remove a part of the stratum corneum. The upper frame 40 has a lowermost sleeve 50, slidable within lower frame 42, and spring loaded by means of compression spring 52 so that the upper frame 40 is biased towards the fully retracted relative position illustrated in Fig. 6.

The upper frame 40 carries within it a cassette 54 having a rotatably mounted reel of adhesive tape 56, guide rollers 58, 60 around which tape from the reel 56

passes, and a take-up roller 62 to receive the adhesive tape after use. A plunger 64 protrudes downwardly from the upper frame 40, and has a lowermost rectangular surface 66 over which the adhesive tape slidably passes, from guide roller 58 to guide roller 60. Plunger 64 moves up and down with upper frame 40 relative to lower frame 42, to bring adhesive tape-bearing lowermost surface 66 into and out of contact with the preselected area of the patient's skin defined by the aperture 46. An electric motor 68 mounted on the upper frame 40 is actuated as the plunger 64 is retracted with upper frame 40 relative to lower frame 42, to drive take-up roller a predetermined amount on each such retraction, so that a fresh length of adhesive tape overlies surface 66 ready for the next application to the patient's skin, i.e. next extension to the position shown in Fig. 5.

Also provided is a light source 70 directed to shine a beam of light at an angle anto the length of adhesive tape 72 last applied to the skin by the lowermost surface 66 of the plunger 64. A light detector 74 is positioned to receive light reflected from adhesive film portion 72, for visual inspection thereof to determine the nature of the stratum corneum portion adhering thereto, and thereby to determine the thickness of stratum corneum removed from the skin area by the operations of the device to that point.

Figure 7 of the accompanying drawings show another but essentially similar preferred embodiment of the invention. The device includes a handle 76 for gripping by the operator's hand, and equipped with a trigger which actuates the aforementioned electric motor to drive both the frames relative to one another and the take-up roller 62 within the cassette 54 to advance a predetermined length of adhesive tape across the bottom surface 66. In this embodiment, a light source 78 is provided to beam a light onto the skin surface through lowermost aperture 46 when the plunger 64 is in the retracted position, and a light detector 80 is positioned to receive light reflected therefrom. In this arrangement, the progress of stratum corneum removal from the predetermined skin surface area is monitored by direct observation of the treated skin area instead of the removed skin layers.

In using the apparatus, a clinician or the patient holds the apparatus in a fixed location against the skin and repeatedly plunges the upper framework, manually or by use of the motor as described, and allows it to retract, causing a portion of stratum corneum to be removed on each retraction. After sufficient stratum corneum has been removed by use of the device according to the invention, a transdermal drug delivery device be applied over the treated area. By use of the devices and processes of the present invention, a wide variety of drugs may be transdermally delivered including those of low to high molecular weight, high polarity, ionically charged

compounds etc., which were previously unsuitable for such administration because they could not penetrate the skin in therapeutic levels. These include proteinaceous and polysaccharide substances.

While the devices of the invention have been described for use in connection with transdermal drug delivery, it will be appreciated that they are useful in other systems where the presence of the stratum corneum acts as a barrier. For example, defects in the epidermis or dermis of a patient's skin can be treated with a therapeutic agent which penetrates the outer layers but does not need to enter the general circulation. Examples include skin carcinomas, which may be located in the dermis or epidermis. In addition, the devices may be used in cosmetic applications, where skin blemishes (freckles, etc) originating in the lower skin layers, but visible through the stratum corneum to the skin surface are to be removed. In such uses, not only is the stratum corneum totally removed by successive adhesive film layers, but also layers of epidermis and possibly portions of dermis are removed, until the blemish is also removed.

Another alternative use for the device of the present invention is in removal of portions of stratum corneum and retention for analysis, e.g. for presence of illegal substances in a mammalian body. A description of suitable analysis techniques is to be found in

International Patent Application PCT/US90/06657 Hill, published May 30, 1991. In yet another use of the devices according to the invention, materials can be removed from the body through the port created by removal of the stratum corneum therewith. This can be done by applying over the location of the port an adherent collection patch to collect material diffusing therethrough. Material so collected, i.e. body fluid, can then be analyzed for the presence of foreign substances.

CLAIMS:

1. Apparatus for compromising the stratum corneum of a desired area of a mammalian patient's skin surface, comprising:

a first frame having a bottom plate for placement against the patient's skin, said bottom plate being apertured to expose said defined skin surface area;

a second frame movably connected to said first frame for movement relative thereto between a retracted position and a fully extended position;

a roll of outwardly adhesive film;

a storage reel carrying a storage portion of said adhesive film roll;

a receiving means carrying the lead end of said adhesive film roll;

an applicator carried by said second frame and having an applying surface, the applicator being positioned so that said applying surface extends closely through said aperture when the second frame is in its fully extended position, and is clear of said aperture when the second frame is in its retracted position, said applying surface contacting a portion of the inward surface of said outwardly adhesive film;

means for advancing the adhesive film in predetermined increments relative to said applying surface, from the storage reel to the receiving means, when the second frame is in its retracted position;

each said predetermined increment being at least sufficient to cover the area of said applying surface.

2. Apparatus according to claim 1 wherein the applying surface is rectangular.

3. Apparatus according to any preceding claim wherein the storage reel and the receiving means are both movably connected to the second frame.

4. Apparatus according to any preceding claim wherein the second frame is biased relative to the first frame towards its retracted position.

5. Apparatus according to claim 3 wherein the receiving means comprises a spool rotatably secured to the second frame, and the applicator comprises the outer peripheral faces of said spool.

6. Apparatus according to claim 5 wherein said spool as axially viewed has polygonal symmetry, with a plurality of similar rectangular peripheral faces each of which can be brought into registry with said aperture to act as said applying surface.

7. Apparatus for partial or complete removal of the stratum corneum thickness of a desired area of a mammalian patient's skin surface, comprising:

a first rigid frame having a bottom plate for placement against the skin of the patient and an aperture through said bottom plate to expose said defined skin surface area;

a second rigid frame slidably mounted within said first rigid frame for movement relative thereto between a fully retracted position remote from said bottom plate and a fully extended position proximate said bottom plate;

a cylindrical reel and an applicator roller, for carrying a supply of outwardly adhesive film wound about and extending between said reel and said applicator roller;

the applicator roller as axially viewed having regular polygonal symmetry, with a plurality of substantially identical, rectangular peripheral edge faces;

said reel and said applicator roller being rotatably mounted on said second rigid frame for rotation about respective axes parallel to the plane of said bottom plate and positioned to allow extension of one of the rectangular faces of the applicator roller closely through the aperture in the bottom plate when the second frame is in the fully extended position to press the adhesive film surface on said face into adhesive, peelable contact with said defined area of skin;

means for moving said second rigid frame between its fully retracted and fully extended positions while said bottom plate remains in position against the skin of the patient with said defined skin surface area exposed through said aperture; and

means operable when said second rigid frame is advanced from its fully retracted to its fully advanced position to rotate said applicator roller, to advance the next adjacent peripheral rectangular face of the applicator roller, carrying fresh adhesive film, to extend through said aperture.

8. Apparatus according to claim 7, wherein said reel and said applicator roller are each mounted for rotation about a respective transverse spindle fixedly mounted to said second rigid frame, the axis of the roller spindle being between the bottom plate and the axis of the reel spindle, parallel to the axis of the reel spindle and aligned therewith in the direction of movement of the second rigid frame, and both said axes being perpendicular to said direction of movement.

9. Apparatus according to claim 8, wherein first corresponding ends of each respective spindle are fixedly mounted to said second rigid frame, and said first rigid frame includes a channelled guide for restraining said reel and said roller against transverse movement while

permitting movement of the spindles there-along in the direction towards and away from the bottom plate.

10. Apparatus according to claim 7, wherein said means for moving said second rigid frame comprises a plunger extending centrally from the top of said second rigid frame and a compression spring associated with said first rigid frame operable to exert a restoring force against said plunger when said second rigid frame is in an extended position.

11. Apparatus according to claim 8, wherein said means operable to rotate said applicator roller comprises [an n-toothed] a toothed ratchet wheel affixed at one end of and coaxial with said roller and a spring loaded pawl affixed to said first rigid frame for coaction with a tooth of said ratchet wheel as said rigid frame is moved from its fully retracted position towards its fully extended position, the ratchet wheel having a number of teeth corresponding to the number of peripheral rectangular faces of the applicator roller.

12. Apparatus according to claim 7 wherein each rectangular face of said roller is convexly curved.

13. Apparatus according to claim 8, wherein the applicator roller has five said rectangular faces, and each of the five rectangular faces is a square of about 1" long

on each side.

14. Apparatus according to claim 7, wherein said bottom plate presents along the perimeter of the aperture therethrough a thin and narrow downwardly projecting serrated ridge for preventing substantial upward motion of the patient's skin outside of said defined skin surface when a surface portion of said adhesive film is removed from contact with the defined skin surface area by retraction of said second rigid frame.

15. Apparatus according to claim 7, wherein said reel, roller and supply of adhesive film are provided together in an integral cassette unit for removable engagement in the apparatus.

16. Apparatus according to any of claims 1 - 5 wherein the receiving means comprises a reel rotatably mounted on said second frame.

17. Apparatus according to claim 16 wherein the means to move the adhesive film relative to the applying surface comprises a motor actuatable to rotate said reel a predetermined amount to bring a completely fresh surface portion of said adhesive film into contact with said applying surface.

18. Apparatus according to claim 17 wherein said

motor is manually actuatable when the second frame is in the retracted position.

19. Apparatus according to any preceding claim, further including inspection means adapted to view the adhesive surface of said adhesive film after it has passed over said applying surface.

20. Apparatus according to claim 19 wherein said inspection means comprises a light source beaming light at said adhesive surface of the adhesive film, and a light detector receiving the beamed light after reflection from said adhesive surface.

21. Apparatus according to any of claims 1-18, further including inspection means adapted to view the surface underlying said aperture in the bottom plate.

22. Apparatus according to claim 21 wherein said inspection means comprises a light source beaming light at said underlying surface, and a light detector receiving the beamed light reflected therefrom.

23. Process for accessing mammalian skin locations below the stratum corneum, which comprises:

(i) selecting an area of skin surface of a mammalian patient;

(ii) applying to said selected area the apparatus of claim 7, with the lower face of said bottom place against the skin of the patient and said aperture superposed over the selected area thereof;

(iii) activating said means for advancing said second rigid frame to bring it to fully extension with a fresh adhesive film surface on said roller in contact with said selected area of the skin surface;

(iv) activating said means for retracting the said second rigid frame to remove said film surface with an adhered layer of stratum corneum from said skin area;

(v) repeating steps (iii) and (iv) until the stratum corneum has been substantially completely removed from the selected area; and

(vi) subsequently applying a covering to said selected area.

24. Process according to claim 23, wherein the subsequently applied covering is a substance delivery means comprising a transdermal drug delivery device.

25. Process according to claim 23, wherein the subsequently applied covering is a substance delivery means comprising a topical drug delivery device or vehicle.

26. Process according to claim 23, wherein the subsequently applied covering is a device for the collection of substances from the body.

27. Process according to claim 23, including the additional step of collecting the removed stratum corneum and analyzing it for foreign substances.

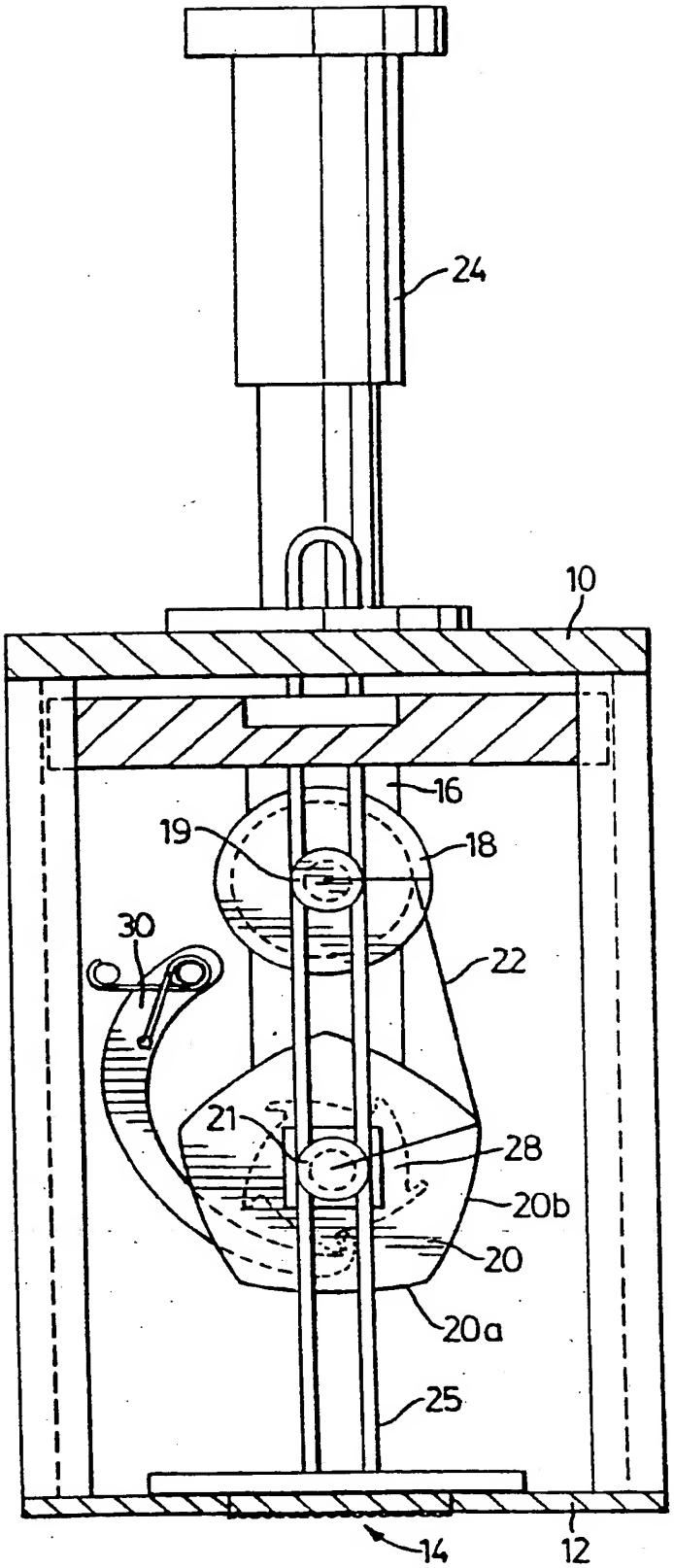

FIG. 1

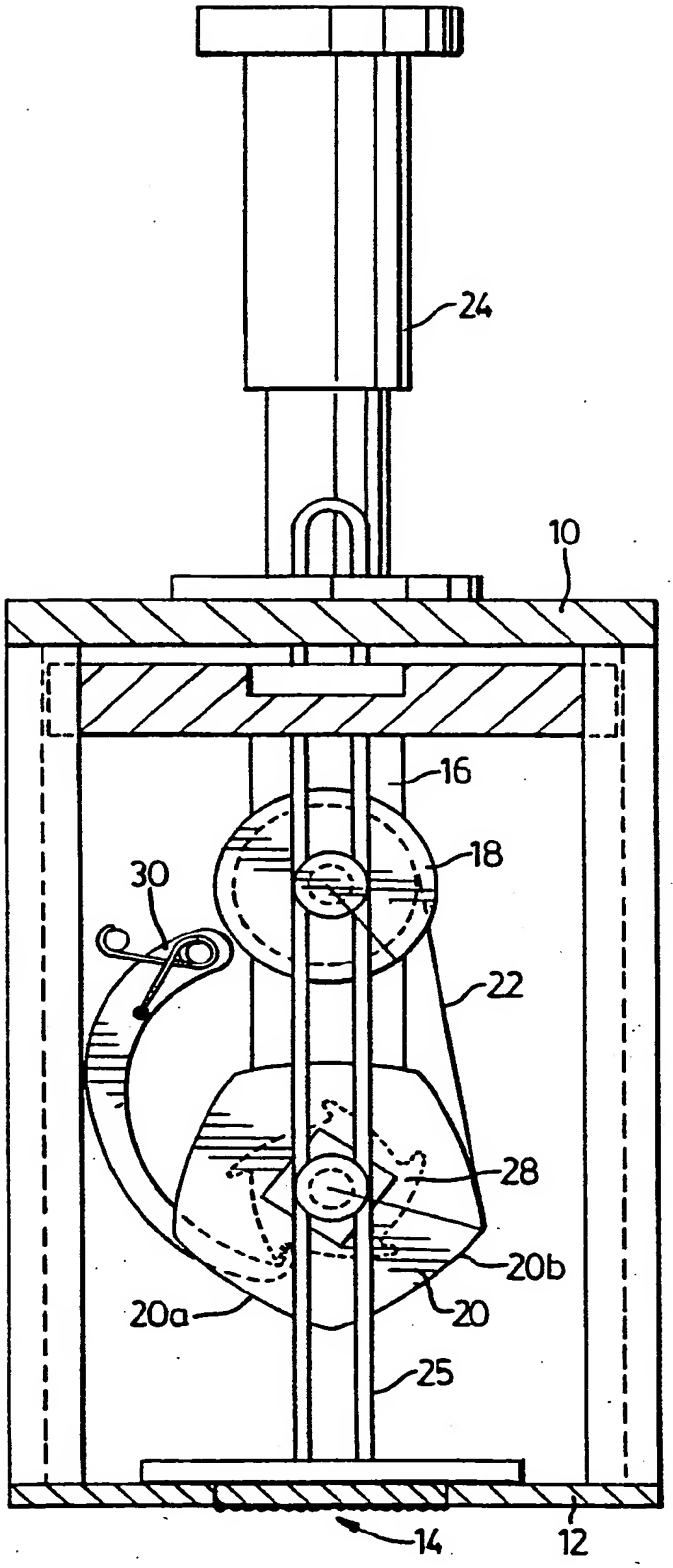

FIG. 2

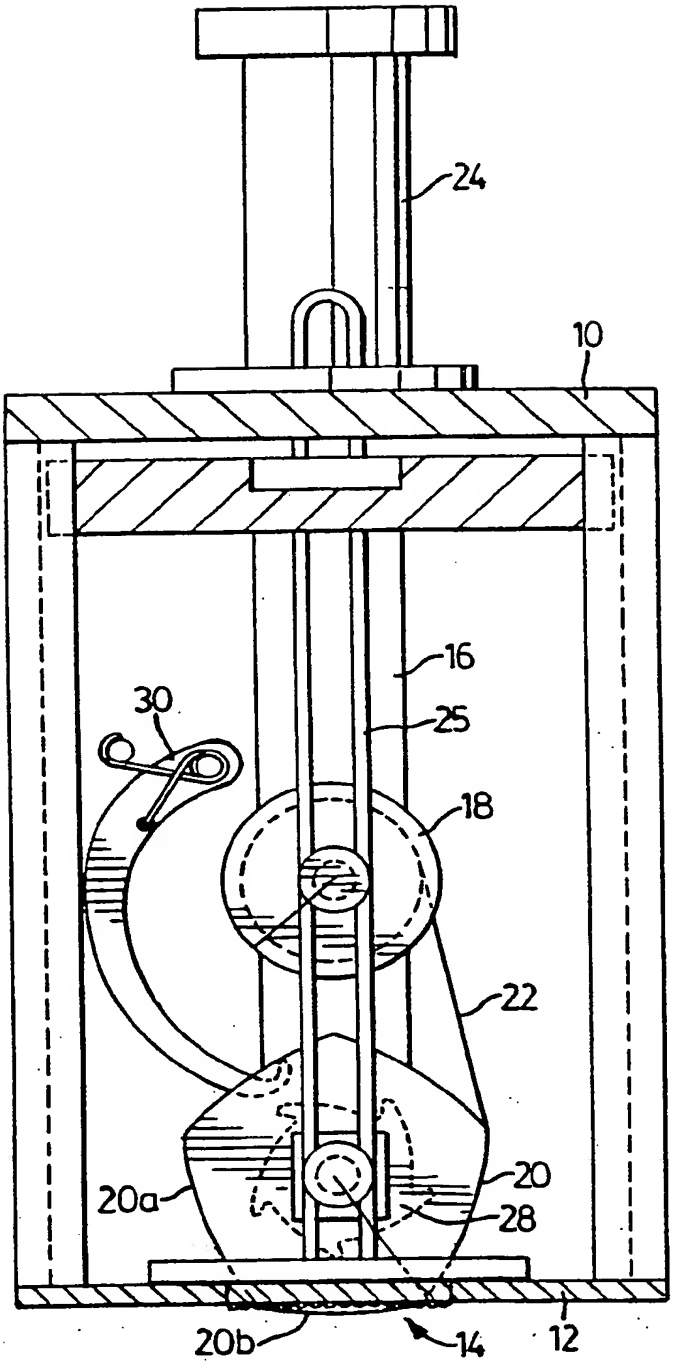

FIG. 3

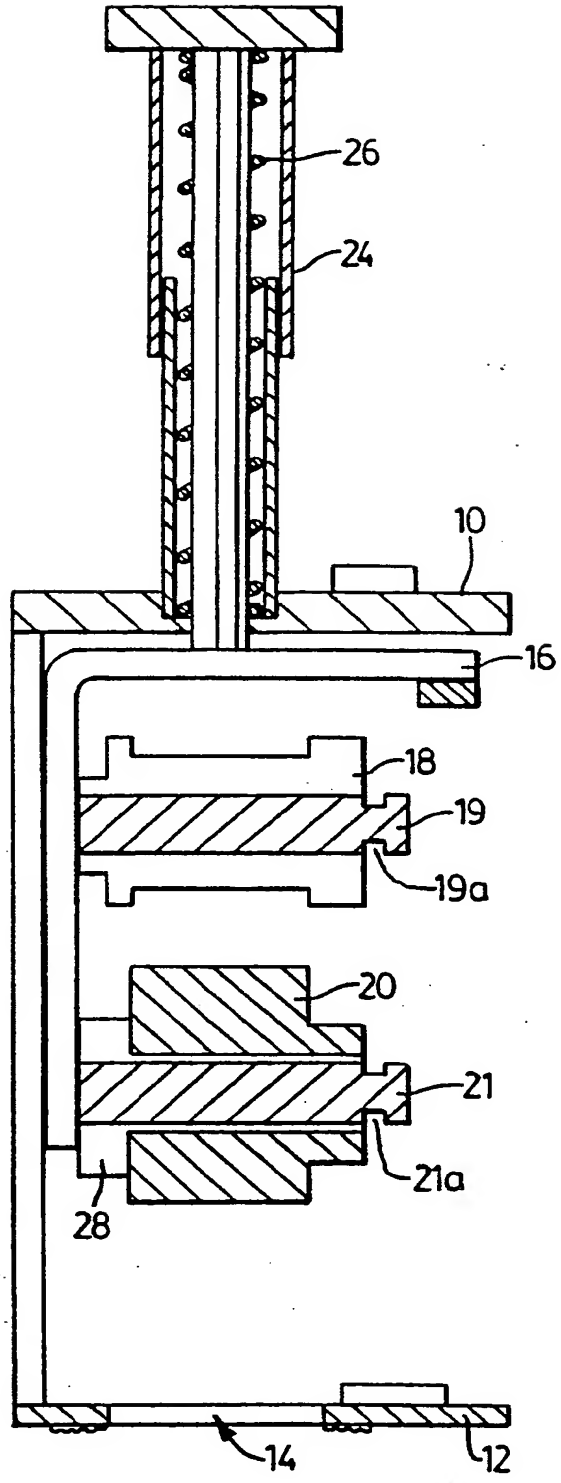

FIG. 4

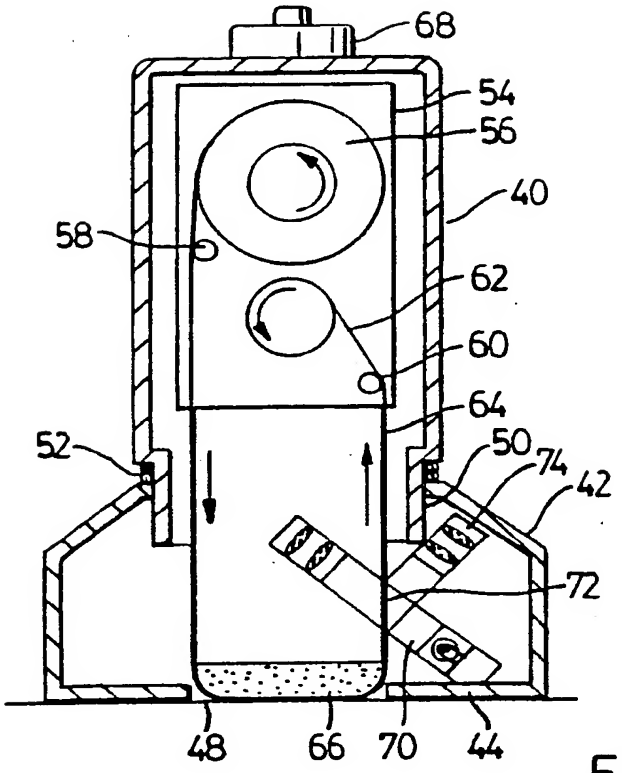
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FIG. 5

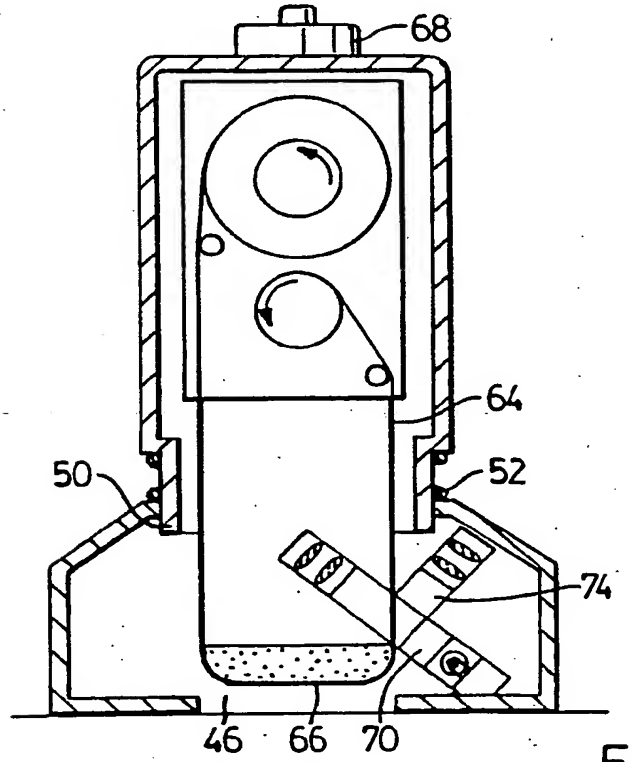
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FIG. 6

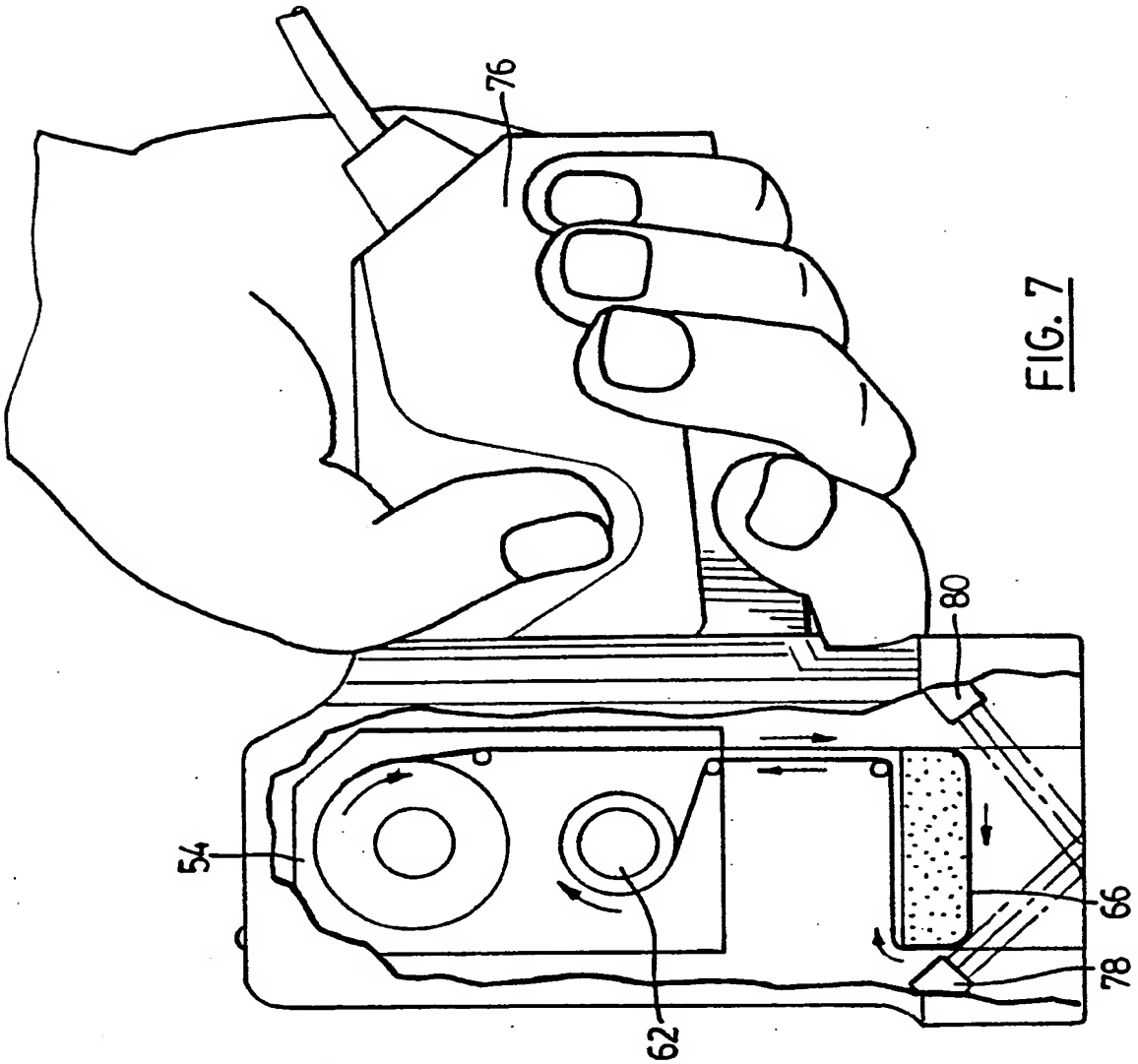

FIG. 7

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/CA 93/00472

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61B17/54

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61M A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,2 819 717 (KUGLER) 14 January 1958 see the whole document	1-7,10, 15-19,23
A	WO,A,92 11879 (PRINCIPAL AB) 23 July 1992 see abstract; figure 21	1,7,23
P,A	US,A,5 190 558 (ITO) 2 March 1993 see claim 1	1,7,23

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 March 1994	24. 03. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Kousouretas, I

INTERNATIONAL SEARCH REPORT

Inter al Application No
PCT/CA 93/00472

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-2819717		NONE		
WO-A-9211879	23-07-92	AU-A-	1984092	17-08-92
		EP-A-	0566605	27-10-93
US-A-5190558	02-03-93	JP-A-	3151951	28-06-91